REMARKS

Claim Amendments

Claims 1, 4, 7, 8 and 10 are amended to cancel subject matter directed to non-elected inventions. Applicants reserve the right to file a continuing application or take such other appropriate action as necessary to protect the invention in the cancelled subject matter.

Claim 7 is also amended to further define the claimed invention. Support for this amendment is found in the specification, for example at page 51, lines 24-25.

No new matter is added.

Sequence Compliance

The Examiner asserts that Figure 2 is not sequence compliant.

Applicants respectfully disagree. As stated in the M.P.E.P. at section 2422.02, the required sequence identifier (i.e. SEQ ID NO: X), can be presented "either in the drawing or in the Brief Description of the Drawings." By way of a Preliminary Amendment filed on July 26, 2004 and received by the USPTO on July 30, 2004, as evidenced by a date-stamped postcard receipt, Applicants amended the Brief Description of the Drawings to recite the appropriate sequence identifiers. For the Examiner's convenience, a courtesy copy of the Preliminary Amendment and the postcard receipt are enclosed for the Examiner.

Priority

The Examiner states that the "instant application has been granted the benefit date, 18 September 2001, from the application 60/322,993" (Office Action, page 3). However, it is Applicants' position that the instant application should be granted the earlier benefit date of 22 August 2001. Applicants have properly claimed their right of priority in the "Related Applications" paragraph of the specification at page 1, lines 2-7. Since the earliest filed application (U.S. Application No. 60/314,046), which supports the instant application, has a filing date of August 22, 2001, Applicants should be entitled to the benefit of this date. Reconsideration is respectfully requested.

Drawings

The Examiner states that the color photographs and color drawings are not accepted unless a petition filed under 37 C.F.R. § 1.84 (a)(2) is granted.

Applicants acknowledge the Examiner's statement and ask that the Petition to Accept Color Drawings under 37 C.F.R. § 1.84 filed July 26, 2004 be granted. For the Examiner's convenience, a courtesy copy of the Petition is enclosed along with a copy of the date-stamped postcard receipt, dated July 30, 2004.

Applicants also note that the specification as filed states the relevant paragraph regarding color drawings at page 7, lines 4-6.

Claim Objections

The examiner objects to Claim 1 as encompassing the non-elected inventions.

As noted above, Applicants have amended Claim 1 (and Claims 4, 7, 8 and 10) accordingly.

Rejection of Claim 7 Under 35 U.S.C. §112, First Paragraph

Claim 7 is rejected by the Examiner under 35 U.S.C. §112, first paragraph as "failing to comply with the written description requirement" (Office Action, page 4). Specifically, the Examiner states that "Claim 7 is broadly drawn, such that it applies to any a genus of nucleic acid that hybridizes under high stringency to SEQ ID NO: 1" (Office Action, page 5). The Examiner further states that "[t]he limitation by hybridization is obviously generic to a considerable number of nucleotides varying in the length of the nucleic acids, the degree of homologies among the sequences, and the biological activities of the encoded polypeptides, which may or may not be involved in the function of IkBNS" (Office Action, page 6). The Examiner concludes that "[c]onsidering the potentially large numbers of polynucleotides encompassed by these claims, the disclosure is not sufficient to show that a skilled artisan would recognize that the applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed" (Office Action, page 6).

Applicants respectfully disagree. A person of ordinary skill in the art would readily appreciate what is encompassed by Applicants' claimed isolated nucleic acid molecules that hybridize under high stringency conditions to SEQ ID NO: 1 or to a nucleic acid sequence that

encodes SEQ ID NO: 2. Hybridization techniques were routine at the time the application was filed. As stated in the M.P.E.P. at §2163:

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. M.P.E.P. §2163 page 2100-173, citing *Hybritech v. Monoclonal Antibodies, Inc.* 802 F.2d 1367 at 1384 (Fed. Cir. 1986).

Furthermore, as elaborated in the M.P.E.P.:

> As explained by the Federal Circuit, "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met . . . even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." M.P.E.P. §2163, page 2100-172, citing *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006).

Applicants' specification as filed, provides sequence information for SEQ ID NO: 1 and SEQ ID NO: 2, and details the activities of the encoded polypeptides (see, *e.g.*, Examples 5, 6 and 7), and the person of ordinary skill in the art readily understands the technique of hybridization. Thus, Applicants' specification as filed adequately demonstrates Applicants' possession of an isolated nucleic acid molecule comprising a sequence that hybridizes under high stringency to SEQ ID NO: 1 or a nucleic acid that encodes SEQ ID NO: 2, wherein said isolated nucleic acid molecule encodes a polypeptide that reduces NF_KB-sensitive reporter activity in Cos cells as claimed in Claim 7. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claim 7 Under 35 U.S.C. §112, First Paragraph

Claim 7 is rejected by the Examiner under 35 U.S.C. §112, first paragraph, as "failing to comply with the enablement requirement" (Office Action, page 7). Specifically, the Examiner asserts that "the claimed invention encompasses an enormous number of nucleic acids" (Office Action, page 7), that "there is no guidance given for nucleic acids that meet the limitations of Claim 7, but are not probes as in Claim 8" (Office Action, page 9), that there are no working examples and a "skilled artisan would not know how to make a nucleic acid which corresponds to the large number of species of nucleic acid encompassed by Claim 7" (Office Action, page 9).

The Examiner cites Wolcott (Clinical Microbiology Reviews, Oct. 1992, p. 370-386) and Gress *et al.* (Mammalian Genome 3:609-619, 1992) in support of the Examiner's assertion that the teachings of Wolcott and Gress *et al.* "cast doubt on the homology of the sequences derived through hybridization methods" (Office Action, page 10).

Applicants respectfully disagree. The enablement requirement of 35 U.S.C. §112, first paragraph, "has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation" (M.P.E.P. §2164.01, citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). Furthermore, the test of enablement "is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue" (M.P.E.P. §2164.01, citing In *re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). Moreover, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (M.P.E.P. §2164.01, citing *In re Certain Limited-Charged Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983)).

A person of skill in the art would know how to make and use an isolated nucleic acid that hybridizes under high stringency to SEQ ID NO: 1 and a nucleic acid sequence that encodes SEQ ID NO: 2, wherein the isolated nucleic acid encodes a polypeptide that reduces NF_KB-sensitive reporter activity in Cos cells. The technique of hybridization is routine in the art (see, *e.g.*, Maniatis *et al.*, "*Molecular Cloning: A Laboratory Manual*" Cold Spring Harbor, 1982, pp. 324-325, attached as Exhibit 1). Furthermore, the specification also describes hybridization conditions (see, *e.g.*, page 20, line 18 – page 21, line 4). The specification also describes a method to determine NF-$_K$B-sensitive reporter activity in Cos cells (see, *e.g.*, page 51, lines 14-25).

Applicants also note that the Examiner has quoted Wolcott and Gress *et al.* out of context. The relevant passages in full read, with Examiner-cited words underlined:

> Solid-phase, or filter, hybridization is usually in the form of dot or colony blots. The basic procedure for filter hybridization is shown in Fig. 1. This format is the oldest and most often used in the research laboratory, but it is subject to more nonspecific background interference than some of the other hybridization formats. (Wolcott, page 372, column 1, citation omitted, emphasis added).

> Similar to early immunoassay technology, the first nucleic acid hybridization studies used radioactive material for labeling nucleic acid probes. The short half-life of most of the radioactive materials (14 days for ^{32}P; 60 days for ^{125}I) and the special handling and disposal requirements make them unsuitable for most clinical laboratories and commercial kit manufacturers. Zeph et al. compared a radioactively labeled probe with three nonradioactively labeled probes; the radioactively labeled probe was more sensitive but produced more false-positive reactions than the nonradioactively labeled probes. (Wolcott, page 371, column 2, citation omitted, emphasis added).

Thus, Wolcott teaches that there are different hybridization techniques, of which filter hybridization is subject to more non-specific background interference than other hybridization techniques. Wolcott also teaches that, when compared with non-radioactively labeled probes, radioactive probes produce more false-positive reactions. A person of ordinary skill in the art would readily understand from Wolcott that using non-filter-based hybridization and non-radioactive probes will reduce both non-specific background interference and false-positive reactions.

In addition, the "complex probes" described by Gress *et al.* which "usually generate a high amount of background and unspecific hybridization" (Gress *et al.*, page 610, column 1) refer to probes that comprise ***total cDNA pools*** derived from different tissues and which are hybridized to ***cDNA libraries*** spotted at high clone density (see Gress *et al.* at page 609, column 2). As explained by Gress *et al.*, "[r]epetitive sequences from nuclear RNA and poly A-tails in cDNA pool probes make the interpretation of hybridization results difficult" (Gress *et al.*, page 610, column 1). In contrast, a person of skill in the art will readily appreciate that Applicants' claimed invention does not require the hybridization of cDNA libraries with complex probes from total cDNA pools because the claims are directed to an isolated nucleic acid molecule that hybridizes to either SEQ ID NO: 1 or a nucleic acid sequence that encodes SEQ ID NO: 2.

Thus, the Examiner's assertion that the teachings of Wolcott and Gress *et al.* "cast doubt on the homology of the sequences derived through hybridization methods" is unfounded. Instead, the teachings of Wolcott and Gress *et al.* reinforce Applicants' position that a person of skill in the art would know how to make and/or use Applicants' claimed invention because it was known in the art that different hybridization techniques can be used to reduce non-specific

background and reduce false positives. Furthermore, as evidenced by Wolcott and Gress *et al.*, such hybridization techniques were routine. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-2 and 4-5 under 35 U.S.C. §102(b)

Claims 1-2 and 4-5 are rejected by the Examiner under 35 U.S.C. §102(b) as being "anticipated by Lamerdin et al. (Genbank Accession NO. AD000864, 22 March 1997)" (Office Action, page 10).

Specifically, the Examiner alleges that "[s]ince SEQ ID NO: 1 contains introns and encodes SEQ ID NO: 2, the GenBank sequence AD000864 ***which comprises SEQ ID NO: 1*** that is capable of encoding SEQ ID NO: 2 and therefore meets the limitations of Claim 1-i" (Office Action, page 11, emphasis added). With respect to Claim 4, the Examiner again asserts that "GenBank Accession Number AD000864, ***comprises SEQ ID NO: 1*** which comprises a nucleic acid that encodes SEQ ID NO: 2" (Office Action, page 11, emphasis added).

Applicants respectfully disagree. Lamerdin *et al.* in GenBank Accession No. AD000864 discloses a linear 39,146 base, single-stranded DNA sequence (see Lamerdin *et al.*, under the line heading "Locus"). This genomic DNA sequence is disclosed by Lamerdin *et al.* to have a coding sequence that encodes for APLP1, having a function described as a "transmembrane glycoprotein related to Alzheimer disease-associated amyloid beta protein precursor" (see Lamerdin *et al.* under the line heading "CDS"). The APLP1 protein disclosed by Lamerdin *et al.* is not identical, or even similar, to SEQ ID NO: 2. Indeed, the 39,146 nucleotide base sequence disclosed by Lamerdin does not comprise SEQ ID NO: 1. The Examiner asserts that Lamerdin *et al.* teach "all of the 15000 bases of SEQ ID NO: 1" and refers to a FASTA Alignment of SEQ ID NO:1 with AD000864 (see Office Action, page 11). However, the FASTA Alignment performed on September 6, 2006, shows that Applicants' claimed SEQ ID NO: 1 is not aligned with AD000864, but instead the ***reverse complement*** sequence of SEQ ID NO: 1 is used. The reverse complement sequence of SEQ ID NO: 1 is ***not*** the same sequence as SEQ ID NO: 1 and does ***not*** encode SEQ ID NO: 2. Instead, the reverse complement of SEQ ID NO: 1 encodes parts of APLP1 as disclosed by Lamerdin *et al.*

Thus, Claims 1-2 and 4-5 are not anticipated by Lamerdin *et al.* because Lamerdin *et al.* does not teach an isolated nucleic acid molecule consisting of SEQ ID NO: 1 or encoding for

SEQ ID NO: 2, nor does Lamerdin *et al.* teach an isolated nucleic acid molecule comprising a nucleic acid sequence that encodes SEQ ID NO: 2. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 7-8 Under 35 U.S.C. §102(b)

Claims 7-8 are rejected by the Examiner under 35 U.S.C. §102(b) as being "anticipated by Rosen et al. (WO/2000/58468A2)" (Office Action, page 12). Specifically, the Examiner alleges that "Rosen et al. teach a sequence of named SEQ ID NO: 17 in the cited patent (page 7 of Sequence Listing), that has 167 contiguous nucleotides in common with SEQ ID NO: 1 of the instant application. This sequence can be used as a probe and can be made to hybridize under high stringency conditions" (Office Action, page 12).

Applicants respectfully disagree. Rosen *et al.* do not teach an isolated nucleic acid molecule or a probe consisting of a nucleic acid that hybridizes under high stringency conditions to SEQ ID NO: 1 or a nucleic acid sequence that encodes SEQ ID NO: 2. The sequence disclosed by Rosen *et al.* is 2,253 bases long, of which the Examiner asserts that the sequence has "167 contiguous nucleotides in common with SEQ ID NO: 1" (Office Action, page 12). Clearly, a person of ordinary skill in the art will recognize that a nucleic acid sequence having only 167 nucleotides out of 2,253 nucleotides (i.e., only 7.4%) in common with SEQ ID NO: 1 will not hybridize under high stringency conditions to SEQ ID NO: 1. Such a low identity of a nucleic acid sequence does not hybridize to an isolated nucleic acid molecule under high stringency conditions. Furthermore, the Examiner asserts that the Rosen *et al.* sequence has "167 contiguous nucleotides ***in common***," (Office Action, page 12, emphasis added) indicating that these 167 nucleotides are identical and thus, would not hybridize to SEQ ID NO: 1 because they are not a reverse complementary sequence of SEQ ID NO: 1, which would be necessary to meet the claim limitations. Thus, the sequence disclosed by Rosen *et al.* cannot anticipate Applicants' claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3 and 6 Under §103(a)

Claims 1-3 and 6 are rejected by the Examiner under 35 U.S.C. §103(a) "as being anticipated [sic] by Lamerdin et al. (GenBank Accession No. AD000864 22 March 1997),"

(Office Action, page 13). The Examiner again states that the "Lamerdin et al. sequence teaches all of the 15000 bases of SEQ ID NO: 1, thus GenBank Accession NO. AD000864 comprises SEQ ID NO: 1 and a nucleic acid that encodes SEQ ID NO: 2" (Office Action, page 13). The Examiner further states that "[i]t would have been obvious to the person of ordinary skill in the art at the time of the invention was made to utilize a portion of the sequence of GenBank Acc# AD000864 that contains all of the exons of a gene" (Office Action, page 14). Further, the Examiner states that "[t]he person of ordinary skill in the art would have been motivated to make those modifications because it is a DNA sequence that contains all of the coding sequence of IKBNS" (Office Action, page 15). The Examiner concludes that "[t]he skilled artisan would have had a reasonable expectation of success in utilizing the nucleic acid sequence of Lamerdin et al. in place of the nucleic acid sequence of SEQ ID NO: 1 or in place of the nucleic acid sequence which encodes SEQ ID NO: 2, because the Lamerdin sequence can be substituted for any functions that the sequences of the instant application are put to use" (Office Action, page 15).

Applicants respectfully disagree. As discussed above, Lamerdin *et al.* does not teach or suggest an isolated nucleic acid molecule consisting of SEQ ID NO: 1 or encoding for SEQ ID NO: 2. The Lamerdin *et al.* sequence is a 39,146 base, single-stranded nucleic acid sequence taught by Lamerdin *et al.* to encode for APLP1. Applicants' claimed SEQ ID NO: 1 is not disclosed by Lamerdin *et al.*, and as illustrated by the Examiner in a FASTA alignment performed on September 6, 2006, only the reverse complement sequence of SEQ ID NO: 1 is comprised in the Lamerdin *et al.* sequence. The reverse complement of SEQ ID NO: 1 is ***not*** the same as SEQ ID NO: 1 and does not encode the same polypeptide as SEQ ID NO: 1. A person of ordinary skill in the art would not "at once envisage" Applicants' claimed invention. There is no teaching or suggestion by Lamerdin *et al.* of an isolated nucleic acid molecule consisting of a nucleic acid sequence that encodes SEQ ID NO: 2. The Examiner is using impermissible hindsight afforded by Applicants' claimed invention by asserting that "[t]he person or ordinary skill in the art would have been motivated to make those modifications because it is a DNA sequence that contains all of the coding sequence of IKBNS" (Office Action, page 15). Prior to Applicants' invention, the person of ordinary skill in the art had no knowledge of IκBNS and thus, would not be motivated to take the Lamerdin *et al.* sequence, select a specific sequence

within the 39,146 bases and convert it to another sequence which a reverse complementary sequence, in order to arrive at Applicants' claimed invention. Lamerdin *et al.* fails to teach or suggest all of the claim limitations of Claim 1, and the claims dependent thereof, and thus, a *prima facie* case of obviousness is not established. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections of Claims 10-12 Under 35 U.S.C. §103(a)

Claims 10-12 are rejected by the Examiner under 35 U.S.C. §103(a) "as being anticipated [sic] by Lamerdin et al. (GenBank Accession No. AD0008624 22 March 197) in view of Liu et al. (Current Biology, 19 November 1998, 8:1300-1309)" (Office Action, page 15).

Specifically, the Examiner alleges that the "Lamerdin et al. sequence teach all of the 15000 bases of SEQ ID NO: 1" (Office Action, page 15). Further, the Examiner states "Lamerdin et al. does not directly teach the use of a plasmid or vector. However, the isolated genomic DNA of GenBank Accession No. AD000864 would have been cloned in a vector of same kind. Liu et al. teach the Univector plasmid-fusion system which can accommodate large DNA inserts and shuttle the inserts between various cloning vectors" (Office Action, page 16). The Examiner also states that "Liu et al. teach 'coding regions of genes could be placed under control of regulated promoters" (Office Action, pages 16-17), and that "Liu et al. teach 'Expression of UPS-derived constructs in mammalian cells'" (Office Action, page 17). The Examiner concludes that "[t]he skilled artisan would have had a reasonable expectation of success generating recombinant host cells comprising expression vectors or plasmids with the nucleic acids of Lamerdin et al. because recombinant host cells comprising expression vectors have been developed, utilized, and marketed for many years. Therefore the vector as taught by Lamerdin et al. and Liu et al. would have been *prima facie* obvious over the method of the instant application" (Office Action, pages 17-18).

Applicants respectfully disagree. As discussed above, Lamerdin *et al.* does not teach or suggest SEQ ID NO: 1 or a nucleic acid sequence that encodes SEQ ID NO: 2. The combination of Lamerdin *et al.* with Liu *et al.* instead teaches or suggests a vector comprising a 39,146 nucleotide sequence that encodes APLP1. A person of ordinary skill in the art would not at once envisage Applicants' claimed invention from these teachings. Therefore, a *prima facie* case for

obviousness has not been established. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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